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## **Are patterns of bone loss in anorexic and postmenopausal women similar? Preliminary results using high resolution peripheral computed tomography**

Milos, Gabriella ; Häuselmann, Hans-Jörg ; Krieg, Marc-Antoine ; Rüeggsegger, Peter ; Gallo, Luigi M

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**Are patterns of bone loss in anorexic and postmenopausal women similar?**  
**Preliminary results using high resolution peripheral computed tomography**

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## **Abstract**

This study intended to compare bone density and architecture in three groups of women: young women with anorexia nervosa (AN), an age-matched control group of young women, and healthy late postmenopausal women. Three-dimensional peripheral quantitative high resolution computed-tomography (HR-pQCT) at the ultradistal radius, a technology providing measures of cortical and trabecular bone density and microarchitecture, was performed in the three cohorts. Thirty-six women with AN aged 18-30 years (mean duration of AN: 5.8 years), 83 healthy late postmenopausal women aged 70 - 81 as well as 30 age-matched healthy young women were assessed. The overall cortical and trabecular bone density (D100), the absolute thickness of the cortical bone (CTh), and the absolute number of trabecules per area (TbN) were significantly lower in AN patients compared with healthy young women. The absolute number of trabecules per area (TbN) in AN and postmenopausal women was similar, but significantly lower than in healthy young women. This study showed that the degree of deterioration patterns of bone microarchitecture in AN is high, and needs to be deeply analyzed. Especially troubling is the highly significantly reduced number of trabecules in both young AN patients and in healthy late postmenopausal women, compared to healthy young controls.

## **Keywords**

3D-pQCT; microarchitecture of bone; bone loss; anorexia nervosa; osteoporosis; postmenopausal women.

## Introduction

Whereas postmenopausal osteoporosis is a common disease characterized by a systemic deterioration of bone mass and structure, generally starting in the fifth decade of life, bone loss in anorexia nervosa (AN) frequently occurs also in young age. AN usually occurs at a critical time for building up bone mass and as a result of early bone loss is often associated with severely decreased bone mineral density and impairment in bone accrual [1]. Lifetime prevalence of AN in industrialized countries is estimated at 0.5-0.9% in women, and 3-8 times less in men [2, 3]. About 50% of adolescent girls suffering from AN have a bone mineral density Z-score  $< -1$  at one or more sites [4].

According to the Diagnostic Statistical Manual (DSM) of Psychiatric Disorders IV [5], AN is characterized, besides pathological eating behavior and underweight, by fear of gaining weight, distorted body size perception, and amenorrhea in women. Low bone mass and density in AN is due to nutritional deficiencies and alterations in multiple neuroendocrine axes, such as hypogonadism, low insulin-like growth factor-1 and relative hypercortisolemia [1]. In women after menopause, sexual hormone deficiency is assumed to be a precipitating cause of increased bone resorption resulting in osteopenia or osteoporosis. Bone loss in AN, as well as after menopause, often leads to increased bone fragility with a high risk of consequent fractures. Bone microarchitecture and its changes is a key to understand the mechanisms and frequency of fractures. High-resolution peripheral computed tomography (HR-pQCT) is a novel radiologic method that permits high resolution three dimensional measurement of trabecular and cortical bone structure at several locations, mostly at the ultradistal radius and proximal tibia.

In our previous studies, we could demonstrate - by means of HR-pQCT - that AN affected in young women both trabecular and cortical bone, and despite weight increase, improvement of bone density and microarchitecture showed heterogeneous courses at different locations after two years [6, 7]. In general, a comparison between a patient group with altered bone density/structure, and groups of healthy young as well as late postmenopausal subjects will be helpful for a deeper understanding of pathological changes and their impact on bone

structural strength. In the present work, we compare bone density and microarchitecture at the ultradistal radius with HR-pQCT technology in three different female cohorts: anorexic, healthy late postmenopausal women, and healthy young women.

## **Material and methods**

### *Subjects*

*AN patients* were recruited among subjects attending the Psychiatric/Psychotherapeutic Department of the University Hospital of Zurich (USZ). The diagnosis of AN was made according to DSM IV [5] at the Psychiatric Outpatient Department (Section of eating disorders) of the USZ. The AN group consisted of 36 women aged between 18 and 30 years. Pregnant women were excluded from the study. Age, Body Mass Index (BMI), and age at menarche are described in Table 1. All AN patients had a BMI below 17.5 (diagnostic criterion for AN) at recruitment time. However, during the time period between the initial recruitment and the physical examinations, some weight changes occurred. The BMI at the time of examination ranged from 13.1 to 17.9 kg/m<sup>2</sup> (mean  $\pm$  SD: 16.0  $\pm$  1.3). The average age at AN onset was 17.6 years (SD 3.2) and the average duration of the disorder was 5.8 years (SD 3.5). The mean duration of underweight (BMI < 17.5) was 56 months (SD 37) and the mean minimum lifetime BMI was 13.2 (SD 1.7). The mean duration since the last period was 24 months (SD 26). There was no primary amenorrhea in the AN patient group, 64% used oral contraceptives for a mean duration of 41.5 months.

The *postmenopausal control group* was defined as women aged between 70 and 80 years and was recruited consecutively in the Zurich metropolitan area by the Osteoporosis Center of the Department of Rheumatology of the USZ. It consisted of 83 healthy women able to walk and independent for daily activities. These women's median age was 76 years (min 70, max 81 years) and BMI had a median of 23.9 (min 19.4, max 34.6) at examination time. They did neither take any medications for osteoporosis treatment nor supplements, such as calcium or Vitamin D. This group had neither history of hip fractures nor bilateral hip replacements nor metabolic conditions influencing bone density or bone and structure.

All participants completed questionnaires on socio-demographic data, weight condition and anthropometric data and were examined by a rheumatologist. Furthermore, AN patients and healthy young controls reported on eating disorders, (under)weight history, menstruation, use of medication, hormonal substitution or contraceptives, as well as the intake of vitamins, minerals, or calcium products.

The *healthy young control group* was composed by a total of 30 women recruited among students of Medicine and Psychology at the University of Zurich. Inclusion criteria were: age 18-30, no current or lifetime eating disorder, no underweight (i.e. current BMI above 18) and no regular intake of medications (except oral contraceptives), neither bone nor other general diseases. The mean current age and mean age at menarche did not differ from the AN group (see Table 1).

The study was approved by the Ethics Committee of the Psychiatric Department of the University Hospital Zurich. All participants gave written informed consent.

#### *Data acquisition*

Bone mineral density and bone micro-architecture were measured at the ultradistal radius of the non-dominant forearm by means of high resolution multislice three-dimensional peripheral quantitative computer-tomography (HR-pQCT) (Scanco Medical AG, Bassersdorf, Switzerland) [8, 9]. This is a valid methodology for the study of bone microarchitecture, since it measures true volumetric BMD, distinguishes between cortical and trabecular compartments and has adequate resolution to measure cortical and trabecular structure [10]. The measurement protocol included acquisition of a stack of 60 high-resolution CT slices. Slice thickness was 0.28 mm, pixel matrix 512×512 and pixel size 0.17 mm. The recordings were reformatted in order to obtain consecutive cross-sectional slices in 0.17 steps mm in the axial direction thus yielding cubic voxels (0.17×0.17×0.17 mm<sup>3</sup>). Measurements were performed at the Institute for Biomedical Engineering, University of Zurich and Federal Institute of Technology (ETH).

Quantitative parameters were defined as follows:

D100: mean entire bone (cortical and trabecular) density of the ultradistal part of the radius in grams hydroxyapatite equivalence per cm<sup>3</sup> (grHA/cm<sup>3</sup>);

Dcomp: bone density of the cortical part of the bone (grHA/cm<sup>3</sup>);

C.Th: absolute thickness of cortical bone (mm);

Dtrab: density of the trabecular area of the bone (grHA/cm<sup>3</sup>);

Dmeta: density of the sub cortical area of the trabecular bone (grHA/cm<sup>3</sup>);

BV/TV: relative bone volume as part of the total volume (%);

Tb.N: absolute number of trabecules per area (1/mm);

Tb.Th: mean thickness of bone trabecules (mm);

Tb.Sp: mean separation distance between trabecules (mm).

The average short-term precision of the multislice high-resolution 3D-pQCT after repositioning is 1.1% for Dtrab and 1.6% for structural parameters such as TbN [8, 9].

### *Statistical analysis*

All parameters were normally distributed according to Kolmogorov-Smirnov and Shapiro-Wilk tests at a significance level of  $\alpha=0.05$ . Box-plots were produced for each parameter that were tested for group differences by means of ANOVA (factor “group”, *i.e.* AN, postmenopausal and controls) with post-hoc tests with Bonferroni correction. Differences were considered non-significant for  $p>0.05$ , significant for  $p<0.05$ , very significant for  $p<0.01$  and extremely significant for  $p<0.001$ . Statistical tests were performed by means of PASW statistical software package V. 18 for Windows (SPSS Inc. Chicago IL, USA).

### **Results**

Table 1 shows the demographic data of the three groups; table 2 lists the parameter values of bone density and microarchitecture, whereas table 3 shows the significances (p-values) of the parameters according to the post-hoc tests in the ANOVA. The parameter data and the significance of their differences are represented also in the box-plots of Fig. 1.

The HR-pQCT technology at the ultradistal radius could clearly demonstrate that D100 and CTh are significantly lower in anorexic women compared with in healthy young controls.

In AN patients the number of trabecules (Tb.N) and the trabecular separation (Tb.Sp) were highly significantly different from those of the young controls. In healthy young controls, the number of trabecules was significantly higher ( $p < 0.001$ ) and the trabecular separation was significantly lower ( $p = 0.003$ ) but not in healthy late postmenopausal women ( $p = 1.00$  and  $p = 0.112$  respectively) (s. Fig. 1). In addition, healthy late postmenopausal women showed significantly lower values of the following densitometrical and structural parameters at the ultradistal radius compared to both anorexic women and healthy young controls: the integral bone density (D100), the bone density of the cortical compartment (Dcomp), the absolute thickness of the cortical zone (CTh), the density of the trabecular compartment (Dtrab), the density of the sub-cortical area of the trabecular bone (Dmeta), the relative bone volume as part of the total volume (BV/TV) and the mean thickness of the trabecules.

## **Discussion**

In the present study, using HR-pQCT technology at the ultradistal radius, significant differences could be found in bone density and microarchitecture between three local Swiss cohorts: young women with AN, healthy late postmenopausal controls, and healthy young women age-matched with the AN patients: The main finding is the observation that trabecular number is rapidly affected in AN, and that cortical bone is only moderately compromised as compared to healthy young women.

As expected, all bone microarchitectural parameters showed bone deterioration in otherwise healthy late postmenopausal women compared with healthy young women. The integral (cortical and trabecular) bone density of the ultradistal radius was also markedly (D100 only moderately) affected in AN patients compared to young controls, thus confirming that AN patients significantly lose bone mass, a well-known fact reported by several studies over almost three decades [11] [12-14]. Interestingly, we found no significant difference in bone density of the cortical part of the ultradistal radius (Dcomp) and no significant difference in trabecular thickness (TbTh) between anorexic and healthy young women. In young AN patients, the cortical bone density is only marginally affected compared to age matched controls. This fact is in line with our previous work [6]. The extremely significant differences



between young patients with AN and healthy late postmenopausal patients in the subcortical bone and trabecular area evidence the influence of bone degradation due to ageing.

The most alarming finding of this study is the high degree of alteration of the trabecular bone in AN, similar to the degree of alteration in postmenopausal women. Indeed, the values of the parameter TbN lead to the assumption that a similar process of dissolution of whole trabecules might happen already in young patients with AN. These results therefore suggest insidious consequences of AN on the intimate cancellous bone structure, whereas its cortical area, at least in its density appears hardly affected.

Some studies reported that bone loss characteristics of AN are more severe than the commonly seen post-menopausally-induced bone loss (e.g. [15]). The present study cannot fully support this statement while permitting a direct and more differentiated comparison of bone microarchitecture among three key groups: in young AN patients the cortical bone is only marginally affected in comparison to that of healthy young controls, whereas the degradation of the trabecular bone is comparable to that occurring in healthy late postmenopausal women.

Osteoporosis is caused by a bone remodeling disturbance in which bone resorption exceeds bone formation [16]. Whereas trabecular bone is severely affected already after few years (around 6) in AN patients, in postmenopausal women a similar break-down occurs over a longer time span (around 25 years). These findings suggest that the microstructural bone damage in young AN patients is a complex multifactorial process of nutritional deficiencies and alterations along multiple neuroendocrine axes [17].

The present study is to our knowledge the first one using cutting-edge technology to compare bone microarchitecture across different conditions. Furthermore, the use of local cohorts increases the significance of the results, because it minimizes bias due to different environments, ethnicities and cultural and socioeconomic situations.

It must be noted that in this study only the HR-pQCT technology was used and that the three cohorts, above all the otherwise healthy late postmenopausal women, were not characterized by the gold standard dual-energy X-ray absorptiometry (DXA) and the question

whether this group is representative for late postmenopausal women cannot be fully answered. On the other hand, DXA technology does not distinguish between cortical and trabecular compartments, whereas HR-pQCT is an appropriate and valid method that assesses bone microstructure [18, 19]. A further limitation of this study is that current or lifetime eating disorders was assessed in the young controls but not in postmenopausal women. This should not affect our results because the prevalence of anorexia nervosa in the general population is low, and even a hypothetical presence of a few postmenopausal subjects with a history of AN would very likely not change the results. Some clues to pathogenesis could be provided if a further comparison group of recovered AN women would be analyzed. In order to better understand the pathophysiology of bone loss in AN, future studies should beside HR-pQCT methodology also collect the numerous endocrinological parameters implicated in bone metabolism [17].

## **Conclusion**

By using HR-pQCT technology, it was possible to observe that the trabecular number is rapidly affected in AN, and that - alarmingly - the degree of the alterations of this bone compartment is comparable with the situation in postmenopausal women. On the contrary, the cortical and subcortical bone of patients with AN was less severely compromised in comparison with healthy postmenopausal women. This data underlines the potentially insidious effects of AN on bone in young patients. Prospective studies should clarify the mechanism and the reversibility of these processes on the bone intimate structure.

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## References

- [1] Misra M, Klibanski A. The neuroendocrine basis of anorexia nervosa and its impact on bone metabolism. *Neuroendocrinology* 2011;93: 65-73.
- [2] Hudson JI, Hiripi E, Pope HG, Jr., Kessler RC. The prevalence and correlates of eating disorders in the national comorbidity survey replication. *Biol Psychiatry* 2007;61: 348-58.
- [3] Preti A, Girolamo GD, Vilagut G, Alonso J, Graaf RD, Bruffaerts R, Demyttenaere K, Pinto-Meza A, Haro JM, Morosini P. The epidemiology of eating disorders in six European countries: Results of the ESEMeD-WMH project. *J Psychiatr Res* 2009.
- [4] Misra M, Aggarwal A, Miller KK, Almazan C, Worley M, Soyka LA, Herzog DB, Klibanski A. Effects of anorexia nervosa on clinical, hematologic, biochemical, and bone density parameters in community-dwelling adolescent girls. *Pediatrics* 2004;114: 1574-83.
- [5] American, Psychiatric, Association. *Diagnostic and Statistical Manual of Mental Disorders TR*. 4th Text Revision ed. Washington, DC: American Psychiatric Association; 2000.
- [6] Milos G, Spindler A, Ruegsegger P, Seifert B, Muhlebach S, Uebelhart D, Hauselmann HJ. Cortical and trabecular bone density and structure in anorexia nervosa. *Osteoporos Int* 2005;16: 783-90.
- [7] Milos G, Spindler A, Ruegsegger P, Hasler G, Schnyder U, Laib A, Gallo LM, Uebelhart D, Hauselmann H. Does weight gain induce cortical and trabecular bone regain in anorexia nervosa? A two-year prospective study. *Bone* 2007;41: 869-74.
- [8] Laib A, Hildebrand T, Hauselmann HJ, Ruegsegger P. Ridge number density: a new parameter for in vivo bone structure analysis. *Bone* 1997;21: 541-6.
- [9] Laib A, Hauselmann HJ, Ruegsegger P. In vivo high resolution 3D-QCT of the human forearm. *Technol Health Care* 1998;6: 329-37.

- [10] Sornay-Rendu E, Boutroy S, Munoz F, Delmas PD. Alterations of cortical and trabecular architecture are associated with fractures in postmenopausal women, partially independent of decreased BMD measured by DXA: the OFELY study. *J Bone Miner Res* 2007;22: 425-33.
- [11] Rigotti NA, Nussbaum SR, Herzog DB, Neer RM. Osteoporosis in women with anorexia nervosa. *N Engl J Med* 1984;311: 1601-6.
- [12] Baker D, Roberts R, Towell T. Factors predictive of bone mineral density in eating-disordered women: a longitudinal study. *Int J Eat Disord* 2000;27: 29-35.
- [13] Grinspoon S, Thomas E, Pitts S, Gross E, Mickley D, Miller K, Herzog D, Klibanski A. Prevalence and predictive factors for regional osteopenia in women with anorexia nervosa. *Ann Intern Med* 2000;133: 790-4.
- [14] Mehler PS. Osteoporosis in anorexia nervosa: prevention and treatment. *Int J Eat Disord* 2003;33: 113-26.
- [15] Mehler PS, Cleary BS, Gaudiani JL. Osteoporosis in anorexia nervosa. *Eat Disord* 2011;19: 194-202.
- [16] Harslof T, Husted LB, Nyegaard M, Carstens M, Stenkjaer L, Brixen K, Eiken P, Jensen JE, Borglum AD, Mosekilde L, Rejnmark L, Langdahl BL. Polymorphisms in the ALOX12 gene and osteoporosis. *Osteoporos Int* 2011;22: 2249-59.
- [17] Misra M, Klibanski A. Bone health in anorexia nervosa. *Curr Opin Endocrinol Diabetes Obes* 2011;18: 376-82.
- [18] Seeman E. Bone quality: the material and structural basis of bone strength. *J Bone Miner Metab* 2008;26: 1-8.
- [19] Liu XS, Shane E, McMahon DJ, Guo XE. Individual trabecula segmentation (ITS)-based morphological analysis of microscale images of human tibial trabecular bone at limited spatial resolution. *J Bone Miner Res* 2011;26: 2184-93.

**Figure 1**

**Comparison between patients with anorexia nervosa, postmenopausal women and young healthy women. Box plots and significances.**

Figure(s)

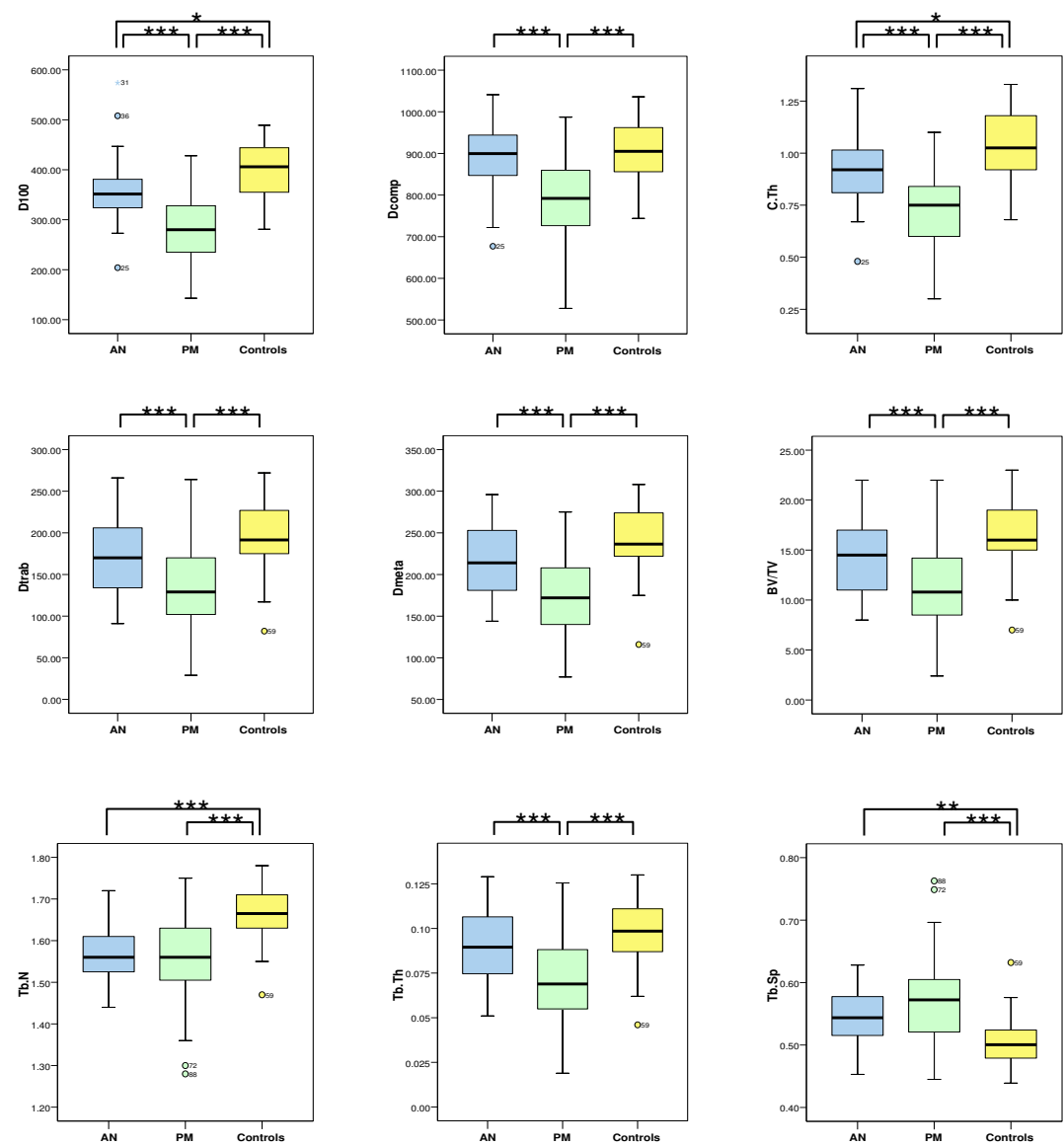


Figure 1.

**Table 1**  
**Demographic data**

<i><b>Parameter</b></i>	<i><b>Anorexia nervosa (AN) (n=36)</b></i>	<i><b>Post-Menopausal (PM) (n=83)</b></i>	<i><b>Control group (Controls) (n=30)</b></i>
Age	23.4 ± 3.7	75.5 ± 3.7	22.8 ± 2.1
Height	165.8 ± 5.7	159.3 ± 5.8	167.1 ± 5.8
Weight	43.9 ± 4.1	63.0 ± 9.4	56.9 ± 4.6
BMI	16.0 ± 1.3	24.8 ± 3.3	20.4 ± 1.5

**Table 2**  
**Comparison between patients with anorexia nervosa, postmenopausal women and young healthy women. Descriptive statistics**

<i><b>Parameter</b></i>	<i><b>AN</b></i>	<i><b>PM</b></i>	<i><b>Controls</b></i>
D100 [gHA/cm <sup>3</sup> ]	358 ± 66	283 ± 65	399 ± 58
Dcomp [gHA/cm <sup>3</sup> ]	888.7 ± 13.3	784.5 ± 10.7	908.1 ± 12.5
C.Th [mm]	0.92 ± 0.17	0.72 ± 0.18	1.04 ± .16
Dtrab [gHA/cm <sup>3</sup> ]	172.06 ± 42.79	134.92 ± 48.33	197.63 ± 45.01
Dmeta [gHA/cm <sup>3</sup> ]	216.42 ± 41.66	174.49 ± 42.52	241.20 ± 41.47
BV/TV [%]	14.39 ± 3.52	11.24 ± 4.02	16.60 ± 3.70
Tb.N [1/mm]	1.57 ± 0.06	1.57 ± 0.10	1.66 ± 0.07
Tb.Th [mm]	0.09 ± 0.02	0.07 ± 0.02	0.10 ± 0.02
Tb.Sp [mm]	0.55 ± 0.04	0.57 ± 0.06	0.50 ± 0.04

**Table 3**  
**Comparison between patients with anorexia nervosa, postmenopausal women and young healthy women. Significances.**

<i><b>Parameter</b></i>	<i><b>AN vs. Controls</b></i>	<i><b>AN vs. PM</b></i>	<i><b>Controls vs. PM</b></i>
D100	0.030 *	<0.001 ***	<0.001 ***
Dcomp	1.000 n.s.	<0.001 ***	<0.001 ***
C.Th	0.018 *	<0.001 ***	<0.001 ***
Dtrab	0.082 n.s.	<0.001 ***	<0.001 ***
Dmeta	0.056 n.s.	<0.001 ***	<0.001 ***
BV/TV	0.064 n.s.	<0.001 ***	<0.001 ***
Tb.N.	<0.001 ***	1.000 n.s.	<0.001 ***
Tb.Th	0.488 n.s.	<0.001 ***	<0.001 ***
Tb.Sp	0.003 **	0.112 n.s.	<0.001 ***